Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendments, claims 27-56 and 102-219 are pending in the application. Claims 57-101 have been canceled without prejudice or disclaimer. Applicants retain the right to pursue the subject matter of the canceled claims in one or more continuing applications. Claims 122-219 have been newly added. The new claims correspond to the subject matter of canceled claims 57-101 and do not include new matter. Accordingly, Applicants respectfully request entry of the amendments.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Pending Claims 120 and 121

Applicants thank the Examiner for acknowledging the pendency of claims 120 and 121. (*See* Paper No. 24, page 2.)

II. The Prematureness of the Final Office Action

Applicants thank the Examiner for removing the finality of the Office Action, dated May 7, 2002. (*Id.*)

III. The Interview of October 9, 2002

Applicants thank the Examiner for extending the courtesy of allowing Applicants' representatives to interview the Examiner, the Supervisory Examiner and the Patent Practice Specialist. Applicants have submitted herewith a "Statement Concerning the Substance of the Interview."

IV. Applicants' Response to the Examiner's Comments Under 37 C.F.R. § 1.111(a)(2)

The Examiner has indicated that the reply filed by Applicants on August 7, 2002 was not entered because "entry of the reply would unduly interfere with the preparation of the Office action." (Paper No. 24, page 2.) The Examiner has stated:

> The second (or subsequent) supplemental reply filed on 07 August 2002 was not entered because entry of the reply would unduly interfere with the preparation of the Office action. See 37 CFR 1.111(a)(2). The examiner spent a significant amount of time on the preparation of an Office action before the reply was received. On the date of receipt of the reply, the examiner had completed the office action of 07 May 2002 of which the instant action is a supplemental.

(*Id.*) Applicants respectfully disagree with the Examiner.

Contrary to the Examiner's assertion, Applicants' reply filed on August 7, 2002 was the first (and only) reply made to the Office Action, dated May 7, 2002—it was not a "second" or "subsequent" supplemental reply to an Office Action. Accordingly, Applicants assert that 37 C.F.R. § 1.111.(a)(2), which relates to the filing of "second" or "subsequent" supplemental replies, is inapplicable.

The Examiner has also stated that he had completed the Office Action, dated May 7, 2002 at the time of receipt of Applicants' reply. This, of course, is true given that Applicants' reply was responsive to the Office Action, dated May 7, 2002. However, this

does not provide a reason as to why it would cause undue interference for the Examiner to prepare a *new* Office Action in response to Applicants' most recent reply.

In view of the above, Applicants assert that the Examiner's application of 37 C.F.R. § 1.111(a)(2) is improper. Applicants believe that the reply filed on August 7, 2002 should have been considered and entered. However, solely to advance prosecution and not in acquiescence to the Examiner's assertions, Applicants have filed the instant Amendment and Reply Under 37 C.F.R. § 1.111 pursuant to the suggestions of the Examiner.

V. Additional Claim Fees

In the reply filed August 7, 2002, Applicants sought to enter new claims 122-219. Applicants included with the reply a check to cover extra claims fees. A copy of the check and fee transmittal form submitted with the August 7, 2002 filing are provided herein as is a postcard indicating receipt of each in the USPTO. However, for reasons explained above, the Examiner has failed to enter the new claims. In the instant reply, Applicants again seek to enter new claims 122-219. As the fee for these extra claims has already been paid, additional fees for extra claims need not be paid with this reply.

However, if additional fees are necessary to prevent abandonment of this application, the Commissioner is hereby authorized to charge Deposit Account No. 19-0036.

VI. Objection to the Claims

The Examiner has indicated that the objection to claims 57, 62-70, 73-81 and 94-100 has been maintained because the claims recite an allegedly improper Markush group. (Paper No. 18, page 2; Paper No. 24, page 2.) For the reasons already on record, Applicants

respectfully disagree with the Examiner. However, in an effort to advance prosecution, claims 57, 62-70, 73-81 and 94-100 have been canceled in favor of new claims 122-219. The new claims do not utilize the Markush format. Accordingly, the Examiner's objection is rendered moot.

VII. Rejections Under 35 U.S.C. § 101

The Examiner has maintained the rejection of claims 27-119 under 35 U.S.C. § 101 because allegedly, the claims are "drawn to an invention with no apparent or disclosed specific and substantial credible utility." (Paper No. 18, page 2; Paper No. 24, page 3.) For the following reasons, Applicants respectfully disagree and traverse the Examiner's rejection.

Applicants point out that claims 57-101 have been cancelled without prejudice or disclaimer and that clams 27-56 and 102-219 are pending on entry of the present amendment. Accordingly, the present rejection will be addressed as it pertains to the pending claims.

Initially, the Examiner is reminded that Applicants need only provide one credible assertion of specific and substantial utility for the claimed invention to satisfy the utility requirement. "When a properly claimed invention meets at least one stated objective, utility under 35 U.S.C. § 101 is clearly shown." *Raytheon v. Roper*, 724 F.2d 951, 958 (Fed. Cir. 1983).

According to the MPEP, a "specific utility" is specific to the subject matter claimed and is to be contrasted with a general utility that would be applicable to the broad class of the invention. (MPEP § 2107.01(I).) A "substantial utility" defines a "real world" use. (*Id.*)

The MPEP states that "[a]n assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition . . . defines a 'real world' context of use. . . ." (*Id.*) A statement of utility is presumed to be credible unless the Examiner establishes that it is more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility. (MPEP § 2107.02(III).)

A. One of ordinary skill in the art would find it credible that the claimed invention has utility in diagnostic applications.

The specification discloses that the claimed nucleic acid molecules have utility in, among other things, diagnostic applications for detecting disease. More specifically, the specification discloses that:

> The present invention also provides diagnostic assays such as quantitative and diagnostic assays for detecting levels of DR3 or DR3-V1 protein. Thus, for instance, a diagnostic assay in accordance with the invention for detecting overexpression of DR3 or DR3-V1, or soluble form thereof, compared to normal control tissue samples may be used to detect the presence of tumors.

(Specification, page 5, lines 10-14.)

The present application is directed to nucleic acids encoding a novel member of the Tumor Necrosis Factor (TNF) family of receptors, specifically, a novel death domain-containing TNF receptor. (Specification at page 1, lines 10-16.) The instant specification discloses that polypeptides encoded by nucleic acids of the invention are expressed by "lymphocytes, fibroblasts, macrophages, synovial cells, activated T-cells, lymphoblasts and epithelial cells." (Specification at page 38, lines 5-8.) Furthermore, the instant specification discloses that nucleic acid molecules of the present invention are involved in "[d]iseases associated with increased cell survival, or the inhibition of apoptosis," including cancers

(such as follicular lymphomas), autoimmune disorders (such as rheumatoid arthritis) and graft versus host disease (GVHD). (Specification at page 38, lines 18-25.)

Based on the complete disclosure that Applicants have provided, one of ordinary skill in the art would understand that the claimed nucleic acids are useful in the diagnosis of diseases and/or disorders associated with aberrant cell survival, *e.g.*, cancers, and are useful in the diagnosis of diseases and/or disorders of the cells in which they are expressed, *e.g.*, lymphocytes. Accordingly, one of ordinary skill in the art would appreciate that the claimed nucleic acids are useful in the diagnosis of diseases associated with aberrant survival of lymphocytes including cancers such as follicular lymphomas, autoimmune disorders such as rheumatoid arthritis, and inflammatory disorders such as GVHD.

Applicants have included with this reply a Declaration Under 37 C.F.R. § 1.132 executed by Dr. Thi-Sau Migone [hereinafter "Declaration"]. Dr. Migone has studied DR3 and is the first named author of the publication entitled "TL1A Is a TNF-like Ligand for DR3 and TR6/DcR3 and Functions as a T Cell Costimulator," published in the peer-reviewed publication *Immunity* in March 2002. (Declaration, ¶ 3.)

In the Declaration, Dr. Migone states that her analysis of numerous experiments performed by herself or by other employees of the assignee indicates that DR3 is expressed at very low levels in normal resting T cells and at very low levels in normal B cells where it is sometimes undetectable. (Declaration, ¶ 21.) Furthermore, Dr. Migone states that Warzocha *et al.*, *Biochem. Biophys. Res. Comm.* 242:376-379 (1998) (previously submitted) shows that DR3 is "abundantly expressed" in a panel of pre-B acute lymphoblastic leukemia cell lines as well as in each of eleven distinct clinical isolates of follicular lymphoma. (Declaration, ¶ 22.) Accordingly, Dr. Migone concludes, "Warzocha confirms that DR3

overexpression is useful as a diagnostic marker for certain lymphoid cancers such as acute lymphoblastic leukemia and follicular lymphoma." (*Id.*)

Dr. Migone further concludes that "[i]n light of the observed expression profile of DR3, together with the experimental results presented in the Warzocha paper, one of ordinary skill in the art would find it credible that DR3 is useful as a diagnostic marker for certain cancers, as disclosed in the Application." (Declaration, ¶ 24.)

Thus, the instant application provides an appropriate example of a situation "where an applicant discloses a specific biological activity and reasonably correlates that activity to a disease condition" and therefore provides a *specific* utility. (M.P.E.P. § 2107.01(I)[2100-32].) Additionally, this utility is *substantial*, since "[a]n assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition ... defines a 'real world' context of use." (MPEP § 2107.01(I) [2100-32].)

Based on the above, it is clear that the claimed invention satisfies the requirements of 35 U.S.C. § 101. The assertion that DR3 can be used in diagnostic applications to detect disclosed cancers is specific and substantial, and as stated by Dr. Migone, one of ordinary skill in the art would find such an assertion credible. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Having established at least one specific, substantial and credible utility for the invention, Applicants need not make any further showings in order to demonstrate that the claimed invention satisfies the requirements of 35 U.S.C. § 101. (*See, e.g.*, MPEP § 2107.02(I); *In re Gottlieb*, 328 F.2d 1016 (CCPA 1964) ("Having found that the antibiotic is useful for some purpose, it becomes unnecessary to decide whether it is in fact useful for

the other purposes 'indicated' in the specification as possibly useful.")). Nonetheless, to clarify the record, Applicants make the following remarks.

B. Cellular Responses to DR3 Activation

The specification discloses that DR3 is a novel death domain-containing TNF receptor, which plays a role in cellular responses including apoptosis and cell proliferation. (*See e.g.*, Specification, page 1, lines 10-16; page 5, lines 15-20; page 6, lines 12-27; page 29, lines 9-16; page 39, lines 3-11; and page 41, lines 21-25.) As discussed below, this disclosure was credible to one of skill in the art at the time the application was filed, and it has been corroborated by post-filing evidence.

In the attached Declaration, Dr. Migone states that prior to the filing date of the present application, signaling through death domain-containing TNF receptor family members was known to cause both apoptosis and NF-κB activation, and that NF-κB activation is responsible for immune cell responses including proliferation. (Declaration, ¶¶ 9-10.) Dr. Migone concludes that the assertion that DR3 may induce apoptosis and proliferation "would have been credible to a scientist in the field of molecular biology." (Declaration, ¶ 11.)

Dr. Migone has further stated that the teachings of Migone *et al.* corroborate the disclosure of the specification with respect to DR3 function. Specifically, Dr. Migone has stated that "[i]n its totality, the Migone paper supports the disclosure of the Application and confirms that the effects of DR3 activation are context specific and that DR3 can act to promote apoptosis in certain cellular environments." (Declaration, ¶ 15; *See also*, Declaration, ¶¶ 8-11, and 14) Thus, Dr. Migone herself has interpreted her own data as consistent with and confirmatory of Applicants' disclosure of DR3 function and activity.

C. Identification of the DR3 ligand, although not necessary to show utility, has subsequently confirmed Applicants' assertions of the cellular role of DR3

The specification teaches that DR3 and/or agonists and antagonists thereof can be used to treat and/or diagnose cancers such as follicular lymphomas, inflammatory diseases such as Graft Versus Host Disease (GVHD), and autoimmune disorders such as rheumatoid arthritis. (*See e.g.*, Specification, page 6, lines 1-11; page 29, lines 9-17; page 38, lines 5-25; page 46, line 20 to page 47, line 3.) As discussed below, these assertions are credible even though the native ligand for DR3 had not yet been identified at the time of filing the instant application.

Migone *et al.* appear to have identified TL1A as the native ligand of DR3. Applicants submit that the identification of the native ligand of DR3 and subsequent studies involving DR3, while not necessary to establish utility of the instant application, serve to *confirm* the disclosure of the specification.

According to Dr. Migone, the Migone *et al.* publication confirms "that: (a) regulation of DR3 activation would modulate the physiological response believed to underlie inflammation and inflammatory diseases such as GVHD; (b) regulation of DR3 activation would regulate the unfettered cellular proliferation that is believed to underlie the development of certain cancers; and (c) regulation of DR3 activation would modulate development of immune responses which are necessary to control viral infections and which underlie autoimmune diseases such as rheumatoid arthritis." (Declaration, ¶ 26.)

Furthermore, as stated by Dr. Migone, Wang *et al.*, Mol. Cell. Biol. 21:3451-3461 (2001) provide further confirmation "that regulation of DR3 activation would modulate immune responses which underlie inflammation and inflammatory diseases such as GVHD,

control of viral infections and certain autoimmune diseases such as rheumatoid arthritis." (Declaration, ¶ 28.)

D. Use of the claimed invention in generating agonistic antibodies against DR3 and DR3-V1 is a specific, substantial and credible utility

In addition to a diagnostic utility, the specification asserts that the claimed invention can be used therapeutically. For example, the specification teaches that the claimed invention can, among other things, be used to generate agonists of DR3. *Such a utility does not require identification of a ligand.* An agonist is defined as an agent, e.g., an antibody, which is capable of increasing DR3 mediated signaling. (Specification, page 6, lines 1-5; page 39, lines 3-11.) Preferably, DR3 mediated signaling is increased to treat a disease wherein decreased apoptosis is exhibited. (*Id.* at page 39, lines 7-11.) According to the specification, specific diseases which exhibit decreased apoptosis include cancers such as follicular lymphoma, autoimmune diseases such as rheumatoid arthritis, viral infections and inflammatory diseases such as GVHD. (*See, e.g.*, page 38, lines 18-21.)

At the time of filing, it was recognized in the art that agonistic antibodies against TNF receptor family members could be used to trigger receptor mediated signaling. For example, Tartaglia & Goeddel, *J. Biol. Chem.* 267: 4304-4307 (1992) (Exhibit 1) demonstrate the use of agonistic antibodies to trigger signaling mediated by TNF-R1, another death domain-containing TNF receptor family member. Indeed, Tartaglia & Goeddel state that "[b]oth polyclonal and monoclonal antibodies directed against human TNF-R1 have been shown to behave as receptor agonists." (Tartaglia & Goeddel at 4304, column 2 (citations removed)). In their own experiments, Tartaglia & Goeddel show that the 55-kDa TNF receptor, stably expressed in mouse L929 cells, was activated specifically by agonist antibodies. (*Id.* at column 1.)

Other studies have shown that agonistic antibodies against TRAIL-R1, another death domain-containing TNF receptor family member, has anti-tumor effects *in vitro* and *in vivo*. For example, Salcedo *et al.*, in a poster which was presented at the 93rd Annual Meeting of the American Association for Cancer Research (AACR) held in San Francisco, California on April 6-10, 2002 (attached as Exhibit 2)[1], found that TRM-1, a human agonistic antibody specific for TRAIL-R1, induced apoptosis in human cancer cell lines *in vitro* and reduced tumor growth in human colon and uterine xenograft models in nude mice. (*See*, Conclusions, columns 5-6.) In addition, TRM-2, a human agonistic antibody specific for TRAIL-R2 (another death domain-containing TNF receptor family member), was found to be effective in reducing or preventing tumor growth in human colon xenograft models in nude mice. (*Id.*)

Applicants submit that the teachings of Tartaglia & Goeddel and Salcedo *et al.* corroborate the assertion that agonists (e.g., antibodies) against DR3 could specifically trigger receptor signaling in the absence of a known receptor ligand. Furthermore, Dr. Migone has stated that the Migone *et al.* and Wang *et al.* "together and individually, provide credible and compelling support" for the use of DR3in the treatment of "diseases such as cancers, including follicular lymphomas; inflammatory diseases, including Graft Versus Host Disease (GVHD); viral infections; and certain autoimmune disease such as rheumatoid

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[1] The abstract of the poster was published as #4240 in the Proceedings of the American Association for Cancer Research, Volume 43 (March 2002), page 856. Throughout this response, Applicants provide the Examiner with both pre-filing date and post-filing date references for no other purpose than to substantiate disclosed utility. In *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995), the Federal Circuit expressly recognized the use of post-filing date declarations and references to substantiate an asserted utility of an invention so long as the reference "pertains to the accuracy of a statement already in the specification." (*Id.* at 1567 n.19.) Thus, Applicants submit that the use of post-filing date references and the data provided therein to support assertions of utility with respect to the instant invention is proper.

arthritis." (Declaration, ¶ 29.)

In view of the above remarks it is clear that at least one assertion concerning utility of the invention is specific, substantial and credible. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the pending claims under 35 U.S.C. § 101.

VIII. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has maintained his rejection of claims 27-119 under 35 U.S.C. § 112, first paragraph. (Paper No. 18, page 5; Paper No. 24, page 3.) The Examiner contends that since the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well-established utility, for the reasons above with regards to the rejection under 35 U.S.C. § 101, one skilled in the art would not know how to use the claimed invention.

In view of the above, the claimed invention has a patentable utility under 35 U.S.C. § 101. The Examiner "should not impose a 35 U.S.C. § 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. § 101 rejection is proper." (M.P.E.P. § 2107(IV) at 2100-28.) Therefore, since the claimed invention complies with the utility requirement of 35 U.S.C. § 101, the rejection of claims under 35 U.S.C. § 112, first paragraph, based on lack of utility of the claimed invention, should be withdrawn.

IX. Claim Rejections Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 27-119 under 35 U.S.C. § 102(b) as allegedly being anticipated by Kitson *et al.*, *Nature* 384:372-375 (1996). (Paper No. 18, page 5; Paper No. 24, page 3.) The Examiner contends that the cited reference is prior art because the priority applications of the present case are unavailable under 35 U.S.C. § 120. The Examiners' rationale is that because the present application doesn't meet the requirements of 35 U.S.C. § 112, first paragraph, the prior applications also do not meet this requirement. Applicants respectfully traverse this rejection.

As discussed above, Applicants believe that the requirements of 35 U.S.C. § 112, first paragraph, have been satisfied for the present application. The requirements of 35 U.S.C. § 112, first paragraph, have also been satisfied for the earlier priority applications. Accordingly, Applicants submit that Kitson is not available as prior art. Reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite

prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

The application has been amended as follows:

In the Claims:

Claims 57-101 have been canceled.

Claims 122-219 have been newly added.